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Studies of the neurogenic bladder

ROGER S KIRBY MA MD FRCS
Consultant Urologist
St Bartholomew's Hospital, London

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Summary

A series of 36 patients with specific neurological lesions affecting those parts of the nervous system thought to be involved in the control of bladder function have been studied by urodynamic, electromyographic and neurohistochemical means and the results compared with those obtained in 20 control subjects. In patients with pelvic nerve injury urethral sphincter electromyography (EMG) revealed abnormal motor units and the density of bladder innervation was significantly reduced ($P<0.01$). By contrast, in patients with distal autonomic neuropathy the innervation of the striated muscle of the urethra was unaffected and although there was an almost total loss of nerves from the bladder muscularis, the subepithelial plexus of nerves was preserved. In patients with progressive autonomic failure and multiple system atrophy, the bladder neck was incompetent in every case and the striated muscle of the urethra was affected by a process of denervation and re-innervation. These findings serve to distinguish patients with autonomic failure from those with idiopathic Parkinson's disease and influence the selection of patients for transurethral surgery.

Introduction

The urinary bladder is an unusual structure in that it is autonomically innervated yet functions under voluntary control. Although it is well known that patients with a variety of neurological diseases suffer disturbances of continence and micturition, the precise ways in which these disorders affect the neurophysiological mechanisms of the bladder are poorly understood. Indeed, when a patient presents with urinary dysfunction it is often difficult to be certain whether there is a neurological basis for the symptoms, or whether they are purely the result of a local abnormality such as bladder outflow obstruction.

In order to throw new light on the subject a series of patients has been studied with well-defined neurological lesions affecting those parts of the nervous system thought to be involved in the control of bladder function. The results were compared with those obtained in a series of age-matched controls.

Patients and methods

The diagnosis and the number of patients investigated in each group are set out in Table I.

TABLE I *Diagnosis of patients investigated in each group*

	No. of patients
Controls	20
Pelvic nerve injury	10
Distal autonomic neuropathy	2
Progressive autonomic failure with multiple system atrophy (Shy–Drager syndrome)	14
Idiopathic Parkinson's disease	10

Each patient underwent urodynamic assessment using previously reported methods *(1)*. In addition, a coaxial needle electrode was inserted into the striated muscle of the urethra; ten individual motor units were isolated and their amplitude and duration recorded *(2)*. At cystoscopy, bladder muscle biopsies were taken and processed to demonstrate autonomic nerves and the density of innervation assessed *(3)*. Statistical analyses were performed using non-parametric methods (Mann–Whitney *U* test) and the level of significance was taken as 5%.

Results

1 PELVIC NERVE INJURY

Patients in this category had all undergone either abdominoperineal excision of the rectum or radical (Wertheim's) hysterectomy. All had suffered prolonged difficulties with micturition following surgery. Urodynamic studies revealed reduced bladder compliance and loss of voluntary detrusor contraction. The bladder neck was incompetent in every patient and voiding was achieved entirely by abdominal straining *(4)*.

Urethral sphincter electromyography (EMG) revealed the presence of abnormal motor units which were of prolonged duration and polyphasic. These findings demonstrate that denervation and re-innervation of the urethral sphincter may occur as a result of extirpative pelvic surgery.

Bladder muscle biopsies in our patients failed to confirm a previous report of Parsons *et al. (5)* that autonomic nerves are absent from the bladder in such cases. Although enzyme-positive nerves were seen in the detrusor muscle, their density was significantly reduced when compared with controls (Fig. 1).

Caution is required in the management of the bladder dysfunction that complicates pelvic surgery. Spon-

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Correspondence to: Mr R S Kirby MA MD FRCS, Consultant Urologist, St. Bartholomew's Hospital, London EC1A 7BE

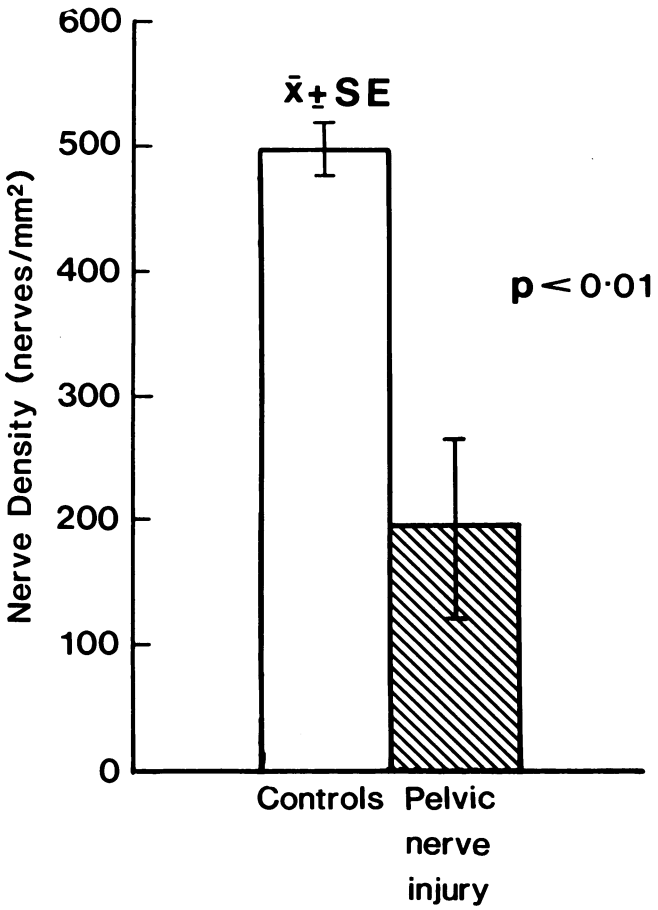

FIG. 1 A bar histogram demonstrating the mean density of innervation of bladder in patients with pelvic nerve injury compared with age-matched controls.

taneous improvement may be anticipated as neuronopraxis resolves, and re-innervation proceeds. Complete restoration of normal function, however, does not always occur. Persistent urinary retention may necessitate transurethral resection of the prostate, but this is associated with a risk of subsequent urinary incontinence, as the only remaining continence mechanism—the distal urethral sphincter—is severely affected by denervation. Intermittent self-catheterisation, or reduction of outflow resistance with α-adrenoceptor blocking agents, such as prazosin, provide an alternative form of management and may sometimes be helpful.

2 DISTAL AUTONOMIC NEUROPATHY

The autonomic nervous system may rarely be affected by an acute peripheral neuropathy similar to that seen in the Guillain–Barré syndrome, but in which somatic motor and sensory nerves are spared. This may take the form of a pandysautonomia, in which both sympathetic and parasympathetic limbs of the autonomic nervous system are involved, or a pure cholinergic dysautonomia, which only affects parasympathetically innervated structures.

In both conditions urinary retention occurs, but there is no incontinence. Urodynamic studies reveal a normal response to bladder filling and a closed bladder neck in cholinergic dysautonomia, but a steep rise in intravesicular pressure and an open bladder neck in pandysautonomia *(6)*. These findings suggest that the sympathetic limb of the autonomic nervous system is involved in bladder muscle relaxation during filling and maintaining proximal urethral competence.

In pandysautonomia and cholinergic dysautonomia sensation of bladder distension is retained, but there is a complete loss of voluntary bladder contraction. Bladder muscle biopsies in both conditions reveal a complete absence of acetylcholinesterase-containing nerves from the muscularis, but a striking preservation of enzyme-positive nerves in the subepithelium. From this it may be surmised that the plexus of nerves lying beneath the bladder epithelium are sensory in function, while those in the muscularis itself are motor nerves.

The management of patients with distal autonomic neuropathy of either variant should be expectant, since at least partial spontaneous recovery is usual. Urinary retention is best managed by intermittent self-catheterisation, because although cholinergic agents induce intense salivation, sweating and bowel activity (as a result of postdenervation supersensitivity) they do not enable micturition to occur.

3 PROGRESSIVE AUTONOMIC FAILURE WITH MULTIPLE SYSTEM ATROPHY

Progressive autonomic failure was first described under the title 'idiopathic orthostatic hypotension' by Bradbury and Eggleston *(7)* though it was Shy and Drager *(8)* who first noted that autonomic failure is associated with degeneration of the intermediolateral column cells of the spinal cord. In the cases they described there was a widespread disturbance of nervous function, which they attributed to selective degeneration of other parts of the brain including the corpus striatum, substantia nigra and the pontine nuclei. The condition was originally known as the Shy–Drager syndrome, but as neurological features they did not recognise have been added, it is now usually known as 'progressive autonomic failure with multiple system atrophy' (PAF+MSA).

The condition has an insidious onset and usually affects individuals in middle age. The first urinary symptoms are frequency and urgency, which soon progress to urge incontinence; men also complain of erectile impotence and failure of ejaculation. Eventually hypotension supervenes and this, together with urinary incontinence, constitutes the most disabling feature of the syndrome.

The cystometrogram in this condition is characterised by involuntary bladder contractions during filling *(9)*. The bladder neck is invariably incompetent (Fig. 2), and the ability to achieve a voluntary bladder contraction is lost early in the disease. The explanation for these findings lies in the degenerative changes that affect the basal ganglia and midbrain; both the corpus striatum and the pontine nuclei have been shown to exert a controlling influence on bladder activity in animals *(10)*. These central effects are compounded by progressive loss of cells from the preganglionic autonomic neurones of the thoracolumbar and sacral spinal segments, which eventually result in a decentralised bladder similar to that seen after pelvic nerve injury.

Patients suffering from progressive autonomic failure and multiple system atrophy are unable to contract the distal urethral sphincter to prevent urinary leakage. Electromyography of the urethra reveals abnormal motor units that suggest that the striated muscle is affected by progressive denervation and attempts at re-innervation (Fig. 3). This seems to be the result of a specific degeneration of a localised area in the sacral

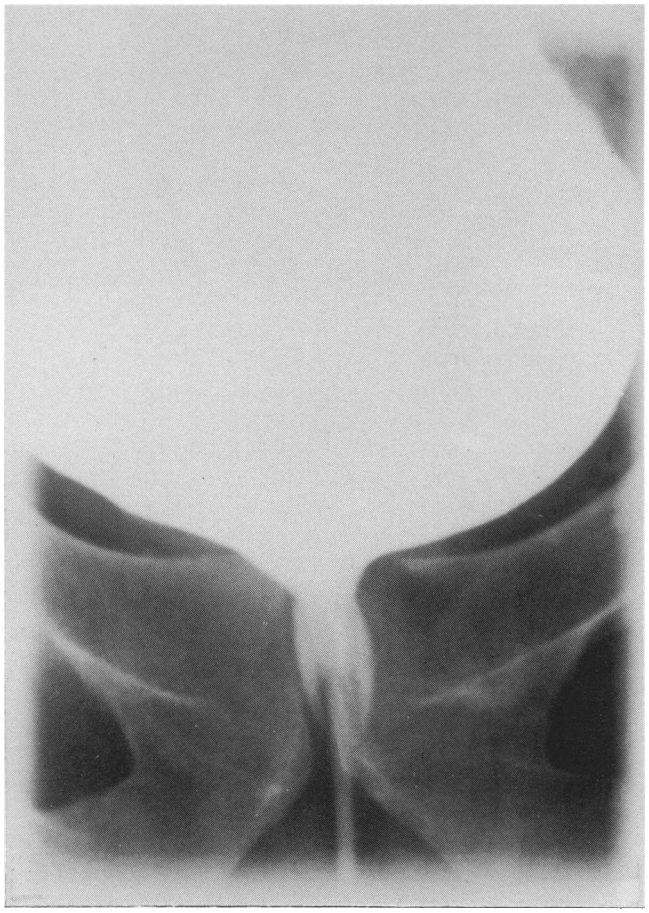

FIG. 2 A cystogram in a patient with progressive autonomic failure and multiple system atrophy demonstrating the characteristic incompetent bladder neck.

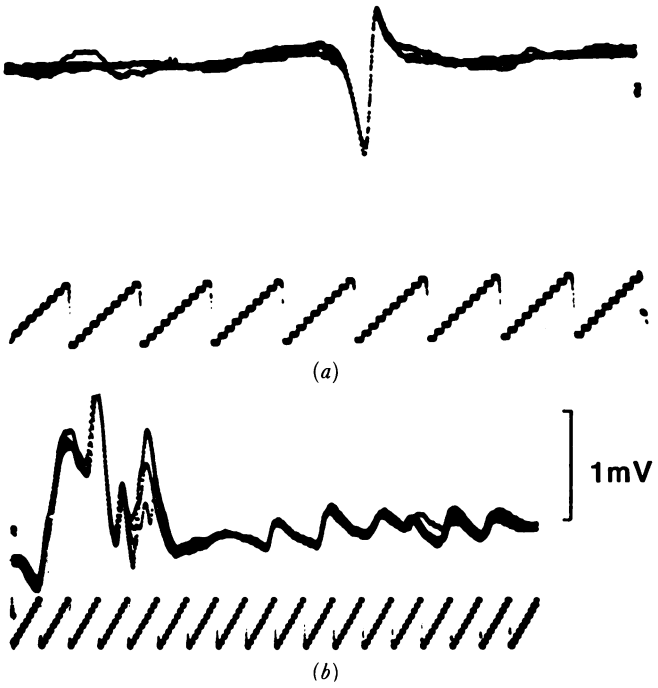

FIG. 3 *a*, An individual motor unit recorded from the striated muscle of the urethra of a control subject. *b*, An individual motor unit recorded from the striated muscle of the urethra of a patient with progressive autonomic failure and multiple system atrophy.

spinal cord known as Onuf's nucleus. These cells have been demonstrated in experimental animals to be responsible for the innervation of both anal and urethral sphincter muscles. Why the cells of Onuf's nucleus should be selectively affected in this condition, while other anterior horn cells are spared is a matter for speculation. The converse seems to apply in motor neurone disease: amid generalised loss of anterior horn cells Onuf's nucleus remains intact. Clearly these cells differ in some fundamental way from other motor neurones.

The striated muscle of the urethra differs from other skeletal muscles in showing tonic electromyographic activity, which persists even during sleep or light general anaesthesia. The only structure that bears close comparison is the cricoarytenoid muscle of the larynx, which is constantly active to maintain abductor tone—and this muscle, too, suffers denervation in progressive autonomic failure with multiple system atrophy. Conceivably it is the property of tonic firing of these neurones—located in Onuf's nucleus in the case of the urethral sphincter, and in the nucleus ambiguous in the case of the larynx—that distinguishes them from the neurones of other skeletal muscles.

Since the degenerative neuronal loss that occurs in progressive autonomic failure with multiple system atrophy cannot be reversed or arrested, treatment of the bladder and sphincter disturbances are at best supportive. Most important is the recognition of the diagnosis and avoidance of transurethral surgery which inevitably exacerbates patients' symptoms. Unfortunately neither anticholinergic nor sympathomimetic drugs are helpful, and the latter carry a risk of hypertension due to the supersensitivity of agonist agents in this condition. Commonly urinary incontinence requires treatment by external urinary appliances in men and intermittent or indwelling urethral catheterisation in women. The poor prognosis of patients suffering this condition generally rules out treatment by implantation of artificial urinary sphincter devices.

4 IDIOPATHIC PARKINSON'S DISEASE

Idiopathic Parkinson's disease is characterised by the selective degeneration of dopaminergic neurones of the basal ganglia. Patients with this condition commonly suffer frequency of micturition and urge incontinence. Occasionally urinary retention occurs, which necessitates catheterisation.

Urodynamic studies in ten of our patients demonstrated a closed bladder neck but confirmed the reports of others *(11)* that involuntary bladder contractions are common in Parkinson's disease. It has been suggested that this is the result of the loss of inhibitory influences of the basal ganglia on the pontine micturition centre. If this is the case then treatment with dopaminergic agents might be expected to reduce the involuntary bladder activity. Ten patients were studied both on and off their antiParkinsonian medications. Although the cystometrograms varied markedly in treated and untreated states, there was no consistent trend towards more stable bladder response to bladder filling when the patients' other Parkinsonian symptoms were controlled by medications *(12)*. This suggests that although the basal ganglia are involved in the control of bladder function, their influence is more complex than simple inhibition of the micturition reflex.

Urethral sphincter electromyography in these patients revealed entirely normal motor units, confirming that the striated urethral muscle is unaffected by denervation in idiopathic Parkinson's disease. This investigation may therefore be helpful in distinguishing patients with idiopathic Parkinson's disease from those with autonomic failure with Parkinsonism; a differential diagnosis which has both prognostic and therapeutic implications. Furthermore, the evidence that distal sphincter innervation is preserved in idiopathic Parkinson's disease suggests that when obstructive benign prostatic hypertrophy coexists, transurethral resection of the prostate may be undertaken with little risk of subsequent incontinence. However, the patient should be forewarned that frequency and urgency of micturition may persist as a result of the involuntary bladder contractions that occur in Parkinson's disease.

Conclusions

These studies throw new light on pelvic nerve injuries and define for the first time the nature of the bladder dysfunction in progressive autonomic failure and in both forms of distal autonomic neuropathy. They also demonstrate the importance of the sympathetic nervous system in the maintenance of bladder neck closure and the parasympathetic system for bladder contraction. Although the neurones controlling striated urethral function are somatic in nature they seem vulnerable in degenerative conditions of the autonomic nervous system. The results also confirm that the basal ganglia are involved in the control of bladder function, but that this control is more complex than the simple inhibitory function that has previously been proposed. Although many questions concerning the neural control of bladder and urethral function are still unanswered, the combination of urodynamic, electromyographic and neurohistochemical techniques now permit a firm diagnosis to be established in the majority of patients afflicted by neurogenic bladder dysfunction. A clearer understanding of the underlying disease processes involved allows selection of those patients who may benefit from surgery from those in whom surgery inevitably exacerbates their condition.

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References

1 Bates CP, Whiteside CG, Turner-Warwick RT. Synchron ous cine/pressure/flow/cysto-urethrography with special reference to stress and urge incontinence. Br J Urol 1970;42:714–23.

2 Fowler CJ, Kirby RS, Harrison MJG, Milroy EJG, Turner-Warwick RT. Individual motor unit analysis in the diagnosis of disorders of urethral sphincter function. J Neurol Neurosurg Psychiatry 1984;47:636–41.

3 Gilpin SA, Gilpin CJ, Dixon JS, Gosling JA, Kirby RS. The effect of age on the autonomic innervation of the bladder. Br J Urol 1986;58:378–81.

4 Kirby RS, Fowler CJ, Gosling JA *et al.* Bladder muscle biopsy and urethral sphincter EMG in patients with peripheral nerve injury to the bladder. J R Soc Med 1986;79:270–3.

5 Parsons KF, Scott AG, Traev S. Endoscopic biopsy in the diagnosis of peripheral denervation of the bladder. Br J Urol 1980;52:455–9.

6 Kirby RS, Fowler CJ, Gosling JA, Bannister R. Urethral dysfunction in progressive autonomic failure and multiple system atrophy. J Neurol Neurosurg Psychiatry 1986;49: 554–62.

7 Bradbury A, Eggleston C. Postural hypotension—a report of three cases. Am Heart J 1925;1:73–86.

8 Shy GM, Drager GA. A neurological syndrome associated with orthostatic hypotension. AMA Arch Neurol 1960;2:511–27.

9 Kirby RS, Fowler CJ, Gosling JA, Bannister R. Urethrovesical dysfunction in progressive autonomic failure with multiple system atrophy. J Neurol Neurosurg Psychiatry 1986;49:554–62.

10 Kuru M. The nervous control of micturition. Physiol Rev 1965;45:425–94.

11 Pavlakis AJ, Siroky MB, Goldstein I, Krane RJ. Neurourologic findings in Parkinson's disease. J Urol 1983;129:80–83.

12 Fitzmaurice H, Fowler CJ, Rickards D, Kirby RS *et al.* Micturition disturbances in Parkinson's disease. Br J Urol 1985;57:652–6.

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